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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,193	10/17/2003	Virgil L. Woods JR.	SDUC1120-1 (041673-3202)	6673

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FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,193	WOODS, VIRGIL L.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *18,19 and 44-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 20-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/17/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/19/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-43, and species 1, pepsin, species 2, carboxypeptidase P and species 3, pH 2.5-3.0 in the reply filed on 05 June 2006 is acknowledged. The traversal is on the ground(s) that Group I-V could readily be searched in a single application because the subject matter of the separate groups are classified in the same class and subclass, Groups I-IV relate to the same method of protein crystallographic structure determination which would also encompass a search of Group V. The requirement for election of species is also traversed because it is asserted that a search of one species would necessarily encompass a search of each of the other species. This is not found persuasive because the fact that groups are classified in the same class/subclass does not necessarily mean that a search for the groups will be co-extensive. For example, Group V, is a method of crystallographic structure determination uses crystals that do not diffract X-rays as a starting point. This limitation will necessitate a different and divergent search from Groups I-IV which imposes an undue search burden upon the examiner.

Regarding the traversal of the requirement for the election of species, Applicants traverse each requirement (e.g. endopeptidase, carboxypeptidase and a pH) and assert that a search for each of the species would not impose an undue search upon the Examiner. Upon further consideration, the Examiner is withdrawing the election of species requirement for the election of a particular pH (claims 22 and 23). However, the Examiner disagrees with Applicants regarding the traversal for the requirement of

electing an endopeptidase and a carboxypeptidase species because each species is distinct and would not produce a co-extensive search. For example, each endopeptidase species has a different structure and mode of function, because for instance cathepsin C is a cysteine protease that cleaves at the site of cysteines whereas thermolysin preferentially cleaves sites with bulky and aromatic residues (Ile, Leu, Val, Ala, Met, Phe) in position P1'. Thus the endopeptidases not only have different structures but they have different modes of action which will not induce a co-extensive search.

It is noted by the Examiner that claims 6 and 12 should not have been withdrawn and will be examined on its merits. Although the claim recites a list of endopeptidases, one of them is pepsin, and thus the Examiner will *initially* examine this claim as reading on the elected species. If, however, the Examiner is unable to find any prior art on pepsin, then the examiner will proceed to the next species listed in the claim until either (a) one of the species in the list is found in the prior art or (b) none of the species are found and thus all of the species are considered free the art. Once a generic claim is found allowable then rejoinder of all the species which are free of the art will occur.

The restriction requirement and election of species requirement is still deemed proper and is therefore made FINAL.

Status of the Application

2. Claims 1-48 are pending. Claims 18-19 and 44-48 are withdrawn from further consideration for being drawn to non-elected subject matter. Claims 1-17 and 20-43 are

subject to examination. N.B. Contrary to Applicants indication that claims 6, 12 and 22 are withdrawn, these claims will be examined. However, examination was not extended to include other non-elected species at this time.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 19 August 2004 has been considered by the examiner. See signed and attached PTO-1449.

Specification

Compliance with Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

The following Figures contain sequences without any SEQ ID NO: and no reference to any SEQ ID NO: in the Brief Description of the Drawings:

> Figures 8, 9, 12, 14A, 15A, 16B, 17B and 18B all contain amino acid sequences with no corresponding Biotech Data in the application.

* The noted sequences are not in any sequence listing and thus, in order to comply with 37 C.F.R. § 1.821 through 1.825, must provide (1) a copy of the sequence listings in both computer readable form (CRF) and paper copy, (2) an amendment directing its

entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Claim Objections

5. Claims 6 and 12 are objected to because of the following informalities: The claims contain non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112 – 2nd paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-17 and 20-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-17 and 20-43 are deemed indefinite because the recitation of 'unstructured region' is ambiguous. To what extent is the protein unstructured and in what state of the protein (e.g. protein in solution or crystalline state) are Applicants referring? Furthermore, is the protein unstructured in the primary, secondary, tertiary or quaternary structures, or all of them? Is it meant that the protein is merely 'unstructured' in the crystal structure? Whereby even this is a false definition because an 'unstructured' region of protein in a crystal still has

structure, it just cannot be modeled into the electron density maps due to high flexibility in the crystal. Unstructured does not equate to highly flexible.

B. Claims 1-17 and 20-42 are deemed indefinite because the use of a 'wherein' clause does not constitute an active method step. This part of the method is determined to be an essential defining feature of the overall method but lacks a positive method step recitation (e.g. subjecting said protein hydrogen exchange analysis to determine at least one unstructured region).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-17 and 20-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for increasing the likelihood that a protein will crystallize by utilizing hydrogen exchange analysis to identify regions that are highly flexible, and then deleting said highly flexible regions which may prevent the crystallization of said protein, thereby increasing the chances that said protein will crystallize, does not reasonably provide enablement for crystallographic structure determination of a protein by possibly crystallizing a protein that has had its highly flexible region removed wherein the highly flexible region was identified by hydrogen exchange analysis. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The claim scope is described above. Simply removing a region from a protein which is highly flexible will not guarantee success in crystallizing a protein. The art of protein crystallography is highly unpredictable and there are many many other factors and variables which must come together in order for successful crystallization of any

protein. McPherson (Eur. J. Biochem., 1990, 189:1-23) states that there are 25 physical, chemical and biological variables that may influence, to a greater or lesser extent, the crystallization of proteins (see p. 13, Table 2 and Factors influencing protein crystal growth). Finding the one condition for successful crystallization of a protein which then leads to successful structure determination is non-trivial and it is well known to rely greatly upon either trial-and-error, even today with the advent of highly automated and high-throughput robotics (see Abstract - Kundrot, Cell. Mol. Life Sci. 2004. 61:525-536), or just plain luck (see Cudney, The Rigaku Journal. 1999, 16(1):1-7). While it is taught in the prior art that it is desirable to cleave off flexible N-terminus or C-terminus in an effort to obtain either higher quality crystals or increase the chances of crystallizing a protein which has been resistant to such efforts, it is also noted that this does not guarantee success (see McPherson, p. 15, 1st column, 2nd to last paragraph). It is merely an avenue which might *improve* the chances successfully crystallizing a proteins. For instance, Dale et al. (Acta Cryst. 1999, D55, 1626-1629) recite a method of deletion mutagenesis in order to successfully crystallize a protein previously resistant to crystallization in the apo- form. The 'unstructured', or highly flexible region of the protein was identified in the three-dimensional crystal structure of the complex and subsequently recombinantly deleted. This lead to crystals of the apo-form of the protein, however, it is noted in the conclusion: "The conclusion that can be drawn from this and previous studies is that mutations can have a dramatic effect on the crystallization properties of proteins and that an *improvement* in crystal quality can generally be obtained. Deletion of flexible regions in proteins provides an additional

method in crystal engineering. An important indication from the various studies is that only a limited number of alterations are required to achieve an *improvement* in the yield or quality of crystals." In factor, the inventors own post-filing work suggests that the method is one which is a method for improving the chances of crystallization by stating: "DXMS analysis was then correlated with the propensity of such targets to crystallize and was further used to define truncations that *improved* crystallization." (see Abstract, Pantazatos et al., PNAS, 2004, 101(3) :751-756).

Thus to recite that the instant method is one of structure determination far exceeds what the claim is enabled for because as stated simply deleting a region of a protein does not guarantee that said protein will crystallize and thus the structure determined. Rather what is enabled is a method for improving the chances that any given protein will crystallize or for improving the chances of enhancing the quality of previously crystallized protein which are of poor quality.

10. Claims 1-17 and 20-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of improving the chances a protein will crystallize by deleting a highly flexible region wherein the highly flexible region is identified by using deuterium hydrogen exchange mass spectrometry analysis which includes progressive degradation of labeled pepsin fragments by using carboxypepsidases analysis followed by protein fragmentation probe maps analysis (progressive proteolysis, see p. 13 of the specification), does not reasonably provide enablement for identifying said highly flexible region using any or all methods of hydrogen exchange analysis. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are described in the preceding paragraph. N.B. MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

The claims are drawn to a method of finding highly flexible regions of protein by utilizing any method of hydrogen exchange analysis. However, methods such as the original method of tritium hydrogen exchange analysis does not allow for the identification of individual amino acids, merely a rough estimation of regions that are solvent exposed (see Englander et al. 1972 and 1973, cited on the IDS). Medium resolution tritium exchange does expand on the original concept by utilizing proteolytic fragments, however, the resolution power of this methods seems limited to 14 amino acid peptides (see Millikarachchi et al., IDS). Because the peptides are significant in size, resolution and assignment to precise amino acids is not possible and thus while these methods might give rough estimates of solvent exposed areas, as stated above in

Section 10, protein crystallography is at best unpredictable and cleaving off amino acids that might be essential to the overall structure integrity of a protein will only serve to hinder the chances of crystallizing any given protein, not improve the chances. Other techniques that utilize deuterium for exchange analysis coupled with for instance mass spectrometry have been described as well (see Smith et al. 1997, Dharmasiri et al. 1996, Englander, 2003 – all cited on the IDS), however, these methods also fail to fully resolve and map the relatively accessibility of each amino acid to solvent because they are limited to using the exact same proteolytic peptide (pepsin), which gives the same peptides and peptide lengths each time. Thus, the methods are limited to mapping small peptides that range from 5-15 amino acids and on the rarer occasions less than ten (see Abstract of Smith et al. 1997, IDS). However, this is not sufficient to give a precise map of the whole protein. Applicants use of "progressive proteolysis" overcomes the limitations of all other hydrogen exchange analysis methods by progressively degrading the pepsin fragments so assignment to amino acid can be achieved. In this way, a clear map can be obtained and exact assignment of each amino acids solvent accessibility can be achieved which gives a good indication of which sections are always solvent exposed and thus flexible. Thus a skilled artisan is assured of not cleaving off potentially vital amino acids involved in the structural integrity of the protein of interest. This resolving power is an essential feature of the invention; however, no other hydrogen exchange analysis techniques is capable of this unambiguous resolution and thus this would invoke considerable undue

experimentation and guess work for any crystallographer wishing to crystallize their protein, which is already an unpredictable science to begin with.

The general methods of the tritium and deuterium hydrogen exchange analyses to this point in time have failed to be able to conclusively resolve and produce functional maps to guide one skilled in the art so as to be able to effectively eliminate the undesirable flexible regions of a protein which prevent it from successfully crystallizing. Thus the scope of the claims exceeds that which is enabled.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-17 and 20-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Dale et al. (cited above).

The claims are drawn to a method of structure determination of a protein by subjecting to crystallization and structure determination one or more modified forms of said protein by deleting at least one unstructured region of said protein, 'wherein' said at least unstructured region is identified by hydrogen exchange analysis. The clause 'wherein' is not an actual method step and thus, the claims read on a method of crystallizing and determining a structure of a protein by deleting an unstructured region determined by any means.

Dale et al. recite a method of deletion mutagenesis in order to successfully crystallize a subunit of DNA gyrase subunit B which was previously resistant to crystallization in the apo- form. The complex of said protein with cyclothialidine was

solved, however, the crystals were both difficult to reproduce and the apo-form not attainable (meeting claim 41). Thus, they determined an 'unstructured', or highly flexible region of the protein in the three-dimensional crystal structure of the complex and subsequently recombinantly deleted said region. The result was the successful crystallization and structure determination of the modified protein. (see Abstract and Sections 2.5 and 3, pp. 1627-28).

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-43 of copending Application No. 10997436. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are obvious variants of one another. The instant claim 1 recites a method for crystal structure determination by deleting an unstructured region of a protein which is determined by hydrogen exchange analysis and then subjecting the protein to crystallization and determining its three-dimensional structure. Claim 1 of the conflicting application recites that is a method of crystallographic structure determination wherein the protein of interest is subjected to two hydrogen exchange analyses wherein the analyses are compared and the unstructured region is lessened and the protein subjected to crystallization and three-dimensional structure determination. These are not seen as patentably distinct methods as it would be obvious to a before and after comparison of a protein in contact

with the crystallizing agent to ascertain if the unstructured region remains unstructured in the crystallizing condition (wherein if it does, the protein is unlikely to crystallize).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.00am to 3.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SMN
29 September 2006

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER